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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61F 2/06, A61L 27/00

A1

(11) International Publication Number: **WO 98/18408**

(43) International Publication Date: 7 May 1998 (07.05.98)

(21) International Application Number: PCT/IB97/01321

(22) International Filing Date: 22 October 1997 (22.10.97)

(30) Priority Data:
964323 25 October 1996 (25.10.96) FI

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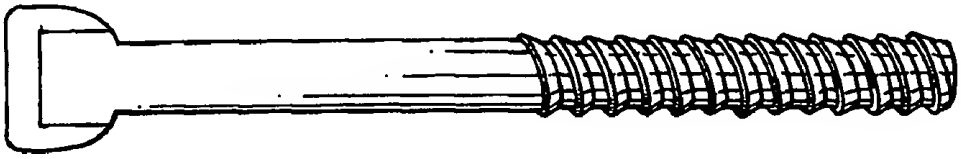
(81) Designated States: AU, CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
With international search report.

(54) Title: SURGICAL IMPLANT



(57) Abstract

The invention relates to a surgical implant, device, or part thereof, comprising a mixed combination of at least: a bioabsorbable portion of a polymeric material and a ceramic particulate portion. The ceramic particulate portion is visible by imaging methods, preferably x–ray positive.

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Surgical Implant

The present invention relates to a surgical implant, device, or part thereof, which is defined in more detail in the introductory part of the appended claim 1.

In surgery, it is known to use at least partly bioabsorbable, elongated, typically tubular, screw-like, thread-like or wire-like surgical implants and devices to support or connect or separate elongated organs, tissues, connective tissues, or their parts from each other. These objects include the skeletal system, various ducts, the intestines, blood vessels, tubes, such as the bronchi, the urinary tracts, the nerves, etc.

In this context, bioabsorbable material refers to a material made of a polymer, copolymer, or a polymer blend whose degradation and/or dissolution in an organism takes place by means of metabolic reactions and/or secretion through the kidneys, lungs, or through the intestines or the skin.

A number of publications describe various tubular screw-like, thread- or wire-like implants and surgical devices to be made of biologically stable or bioabsorbable materials. Implants and devices of this kind are disclosed *e.g.* in the publications US-3,108,357; US-3,155,095; US-3,272,204; US-3,463,158; US-3,620,218; WO 83/03752; WO 84/03035; Daniel and Olding, Plast. Rec. Surg. 74 (1984) 329; WO 90/04982; Van Andersdahl *et al.*, Seminars in Urology, Vol. II (1984) 180; Raja Subra Manian, ASAI Journal 40 (1994) M584; US-4,768,507; US-4,923,470; US-4,973,301; US-4,990,131; US-4,994,066; US-5,019,090; EPO 606 165 A1, WO 94/15583; US-4,950,258; US-5,160,341; and US-4,085,629; US-4,743,257.

Known implants and surgical devices of the above-mentioned or similar type, which are biostable or practically undegradable in tissues, have several disadvantages. Their biostable parts, such as fibers, plastic or metal threadings or rings or tubes or the like, remain in the body even after the organ

or tissue has healed, and therefore implants and devices of this kind can later be detrimental to the patient, causing *e.g.* infections, inflammatory reactions, foreign body reactions, and/or they can release particles or corrosion products or the like, which may further cause harmful reactions in the body.

Many known bioabsorbable implants and surgical devices, e.g. many of those described in the above-mentioned publications as well as those of a corresponding type, do not cause the same kind of long-term complications as biostable implants and surgical devices do, because biodegradable implants and devices are dissolved and degraded biologically in the body, finally leaving the tissues entirely.

A defect with known bioabsorbable implants, however, has been the lack of an effective imaging method. This defect causes problems particularly when there is a need to determine the location of an implant or a device during and after its installation. If visual contact with the area is prevented, the installation can be considerably facilitated with an imaging method, with which the proceeding and installation in its place can be monitored during the operation. These imaging methods may include *e.g.* radiography, ultrasound, magnetography, computer tomography, gamma radiography, spectroscopy, or the like. It is also very important that the implant stays in its place in the installation object, and with a good imaging method, the position of the implant can be easily determined without surgical measures, such as endoscopy.

Bioabsorbable polymers, however, are poorly or not at all visible with imaging methods presently in use. In the present invention, it was surprisingly found that when a ceramic powder or the like is mixed with an implant or corresponding surgical device made of a bioabsorbable polymer, the implant or device can be made visible by imaging methods used in medicine, utilizing x-rays.

When different amounts of ceramic powder or the like, or combinations thereof, are mixed with an implant or a corresponding surgical device made of a bioabsorbable polymer, the implant or device can, depending on the surrounding tissue, be distinguished sufficiently well with an imaging method. Examples of imaging methods are x-ray, ultrasound, magnetography, computer tomography, gamma radiography, spectroscopy, or the like.

Thus, an implant or surgical device according to the invention is, for achieving the above-mentioned purposes, primarily characterized in what will be presented in the characterizing part of the appended claim 1.

Implants or corresponding surgical devices according to the invention can be made of various bioabsorbable polymers, copolymers, or polymer blends, which have been described in a number of publications, for example in: Vainionpää *et al.*, Prog. Polym. Sci. Vol.14, pp. 697—716 (1989); US-4,700,704 (Jamiolkows and Shalaby); US-4,653,497 (Bezwada, Shalaby and Newman); US-4,649,921 (Koelmel, Jamiolkows and Bezwada); US-4,559,945 (Koelmel and Shalaby); US-4,532,928 (Rezada, Shalaby and Jamiolkows); US-4,605,730 (Shalaby and Jamiolkows); US-4,441,496 (Shalaby and Koelmel); US-4,435,590 (Shalaby and Jamiolkows).

The implants or corresponding surgical devices according to the invention can have a structure which is not reinforced, such as made with melt processing techniques or with solution techniques, or they can be reinforced by using e.g. self-reinforcing or reinforcing with absorbable polymer or ceramic fibers.

Some advantageous applications of an implant or corresponding surgical device according to the invention will be presented in the appended dependent claims.

The method of the invention is primarily characterized in what will be presented

in the characterizing part of the independent claim on the method.

The method for manufacturing an implant or a corresponding surgical device according to the invention is based on the fact that ceramic powder or the like is added to the material of the implant or corresponding surgical device to make the implant or corresponding surgical device visible with different imaging methods. Examples of the imaging methods are x-ray, ultrasound, magnetography, computer tomography, gamma radiography, spectroscopy, or the like.

In an advantageous embodiment, the implant or corresponding surgical device is manufactured in a way that the quantity of the ceramic powder or the like, added into the polymer, is different in different parts of the implant or corresponding surgical device. For example, the quantity of the ceramic powder or the like can be greater at the first end than at the second end of the implant or corresponding surgical device. Thus, by this method, the visibility of the implant or corresponding surgical device by the imaging method can be made different at different ends of the implant.

The content of the ceramic powder or the like can gradually decrease in the direction of the longitudinal axis of the implant or corresponding surgical device, or the content of the ceramic powder or the like may be different in the body part as compared with the protruding parts of the implant or corresponding surgical device. Further, ceramic powder or the like can be present only in a certain part or location of the implant or corresponding surgical device in a way that there is no ceramic powder or the like in the other parts of the implant or corresponding surgical device at all. By this method, it is possible to manufacture implants or corresponding surgical devices whose visibility with an imaging method is different in different parts of the implant.

The quantity of the ceramic powder or the like can decrease gradually in the

direction of the transverse axis of the implant. In this way it is possible to manufacture implants or corresponding surgical devices whose visibility with imaging methods is different in the central part than in the outer shell of the piece.

The invention will become apparent from the following description, with reference to the appended figures and drawings presenting some examples on implants or corresponding surgical devices according to the invention, as well as on applications on methods for their manufacture.

Figure 1 X-ray illustration on the abdominal area of a test person. Three stents were placed under the test person on the x-ray table. Seen in the direction from the foot end, there were stents containing 30 wt-% and 10 wt-% barium sulphate, respectively, and an unmixed polylactide stent uppermost.

Figure 2 A spiral (stem) according to Example 2 in a perspective schematic view.

Figure 3 An implant according to Example 3 in a perspective schematic view.

Figure 4 An electron microscopic view on the surface of a polylactide fiber mixed with 30 wt-% barium sulphate, in a 1000x enlarged view.

Figure 5 A schematic view on the spiral according to Example 2, installed in the area of the prostate of a test animal.

Figure 6 An implant according to Example 6 in a perspective schematic view.

Figure 7 A view on the model piece for the stents used in Examples 1 and 4.

Example 1

A blank having the thickness of 1.1 mm diameter was made of commercial polylactide (manufactured by Purac biochem by., Holland) and commercial barium sulphate ($BaSO_4$ by Merck Ltd., Germany) by extrusion (single-screw extruder) and cooled to room temperature on a moving wire. Barium sulphate was mixed with the polylactide, 30 wt-% in comparison with the mass of the polylactide. The blank was drawn after the first wire through four ovens, between which the speed of the draw belts was accelerated when approaching the fourth oven so that the speed difference between the first and last draw belts was eight times. The temperature of the ovens was 140°C. After the fourth oven, the blank was coiled on a roll with a 100 mm diameter. The yield was a 0.4 mm thick oriented polylactide fiber containing 30 wt-% barium sulphate.

The blanks were twisted round a rod with a 2.5 mm diameter in the shape shown in Fig. 7 by heating the blanks with a heat blower during the twisting. The spirals (stents) were heated for 10 minutes on moulds at 100°C temperature in a recirculated air heating chamber, after the moulds had cooled down, the spirals (stents) could be removed from the mould. The stents were packed in a Aluminium-PET foil pouch and gamma sterilized.

As comparison materials, stents made purely of polylactide as well as stents made of polylactide mixed with 10 wt-% barium sulphate were used. These stents were extruded and drawn as well as gamma sterilized in the same way as the polylactide stents containing 30 wt-% barium sulphate described above.

The stents containing 30 wt-% barium sulphate and the stents made of the

comparison material were placed under the back of a volunteer on an x-ray table. The stents were in the order 30 wt-%, 10 wt-% and unmixed polylactide, seen from the foot end of the test person. Radiography was performed on the abdominal area of the test person. From Fig. 1 it clan be clearly seen how visible the stent containing 30 wt-% barium sulphate is even when radiographed through a test person. The spiral structure of the stent is clearly seen in the figure (lowermost stem). The stent containing 10 wt-% barium sulphate is visible above the stent containing 30 wt-% in the radiograph. The stent containing 10 wt-% barium sulphate is visible in the figure, but its spiral structure cannot be seen. The stent containing only polylactide cannot be seen at all in the radiograph.

Example 2

A blank having the thickness of 1.7 mm diameter was made of commercial polyglycolid (Purac biochem by., Holland) by extrusion (single screw extruder) and cooled down to room temperature on a moving wire. The blank was cut into rods of 1 m length. The blanks were drawn at 180°C temperature into an oriented blank with a draw-down ratio 4, yielding oriented polyglycolid blanks with 0.8 mm thickness. The drawn blanks were cut into lengths of 0.6 meters, and both ends of the lengths were sintered with commercial tricalcium phosphate ($Ca_3O_8P_2$, Merck Ltd., Germany) in an area of 10 cm from the end of the blank. In an assay, the content of tricalcium phosphate was 40 wt-% of the content of polyglycolid in the sintered area.

The blanks were twisted to the shape of Fig. 2 around a rod with a 3 mm diameter by heating the blanks with a heat blower during twisting. The ends sintered with tricalcium phosphate were left at both ends of the twisted spiral (stent). The spirals (stents) were heated for 10 minutes on moulds at 100°C temperature in a recirculated air heating chamber. After the moulds had cooled down, the spirals (stems) could be removed from the moulds. The stents were

packed in an Aluminium-PET foil pouch and sterilized with ethylene oxide gas.

As comparison materials, stents made purely of polyglycolid as well as stents made of blanks having ends sintered with 20 wt-% tricalcium phosphate in the mass of polyglycolid, were used. These stents were extruded and drawn as well as sterilized with ethylene oxide gas in the same way as the above-mentioned polyglycolid stents containing 40 wt-% tricalcium phosphate in a range of 10 cm at both ends.

The prepared stents were implanted in dog urethras in the area of the prostate in a way that one end of the stents was at the cervix of the urinary bland and the other end at the urethra side of the sphincter as shown in Fig. 5, and the prostate area of the test animals was radiographed.

The radiographs showed clearly the ends of the stents that contained 40 wt-% tricalcium phosphate at both ends. Also the spiral structure of the stent was shown in the parts where the sintered portion was extended. The unsintered part of the stent was not visible in the radiographs. The stents having ends sintered with 20 wt-% tricalcium phosphate were visible for the ends in the radiographs. However, the spiral structure of these stents was not apparent. The unsintered parts of these stents, and the stents containing only polyglycolid, were not visible in the radiographs.

Example 3

Screw implants shown in Fig. 3 (diameter 2 mm, length 20 mm) were made from a commercial lactide and trimethylene carbonate copolymer (PLA/TMC manufactured by Boehringer Ingelheim, Germany) and calcium iodapate by the injection molding technique in a way that by adjusting the material extrusion rate and pressure, the highest calcium iodopate density was obtained in the core part and the lowest density on the outer surface of the screw implant. An

assay of the implant showed a calcium iodopate density of 40 wt-% in the core and 15 wt-% on the surface of the implant (40/15 wt-%) as compared with the mass of the PLA/TMC. The calcium iodopate content decreased gradually in the direction of the transverse axis of the implant, from the core towards the outer layer. The implants were packed in an Aluminium-PET foil pouch and gamma sterilized.

As comparison materials, implants made purely of PLA/TMC as well as implants made of PLA/TMC with calcium iodopate 20 wt-% in the core and 2 wt-% on the surface (20/2 wt-%) were used. These implants were injection molded and gamma sterilized in the same way as the above-mentioned PLA/TMC implants containing 40/15 wt-% calcium iodopate.

The mixed and unmixed PLA/TMC implants were implanted in the femurs of swines that were used as test animals. Radiography that was performed in the area of installation of the implants did not show the implants made of pure PLA/TMC at all. The implants that were mixed with 20/2 wt-% calcium iodopate were shown in the radiographs as a faint stripe in the bone tissue. The shape of the implant could not be seen. The implants that were mixed with 40/15 wt-% calcium iodopate, were clearly seen in the radiographs so that the core of the implant was clearly apparent and the base part and the spiral part of the implant were slightly less distinguished in the radiographs.

Example 4

Several implants (stents) according to Example 1 were prepared, containing 10 wt-%, 30 wt-% and 50 wt-% barium sulphate as compared with the mass of polylactide. The stents were sterilized with gamma radiation. As comparison material, stents made of pure polylactide were used. The stents were installed in surface veins, biliary tracts and femurs of swines that were used as test animals. The stent installation areas were radiographed.

In the area of the surface veins, all the stents containing barium sulphate were clearly visible, and their spiral structure was clearly distinguishable. The stents containing only polylactide were poorly visible in radiographs on the surface veins, and the spiral structure was not distinguishable.

The stents containing 30 wt-% and 50 wt-% barium sulphate and installed in the biliary tracts were clearly visible in the radiographs. Also the spiral structure of the stent was clearly distinguishable. The stents containing 10 wt-% in the biliary tract were visible in the radiograph, but the spiral structure was not apparent. The stents containing polylactide only, installed in the biliary tract, were not visible in the radiographs.

The stents containing 50 wt-% barium sulphate, installed in the femurs, were clearly distinguished from the bone tissue, and the spiral structure was clearly visible. The stents with a 30 wt-% content, installed in the same area, were visible in the radiograph but the spiral structure was not distinguishable. The stents containing 10 wt-% barium sulphate and only polylactide, installed in the femur, were not visible in the radiographs.

Example 5

Commercial L-lactide and D-lactide copolymer (poly-L,D-lactide, manufactured by Purac biochem bv., Holland) and commercial calcium nitride (Ca_3N_2, Tamro Oy), were used to prepare by extrusion (single screw extuder) a blank with a diameter of 4 mm, which was cooled down to room temperature on a moving wire. The poly-L,D-lactide was mixed with 50 wt-% of calcium nitride in the mass of the poly-L,D-lactide. The blank was cut into rods of 1 m length. The blanks were drawn at 180°C temperature into an oriented blank with a draw-down ratio 4, yielding oriented poly-L,D-lactide blanks of 2 mm thickness. The drawn blanks were cut into lengths of 40 mm which were fumed into screw implants as shown in Fig. 3 (diameter 2 mm, length 20 mm). The implants were

packed in an Aluminium-PET foil pouch and sterilized with gamma radiation.

The comparison materials used were implants made purely of poly-L,D-lactide as well as implants made of poly-L,D-lactide mixed with 30 wt-% calcium nitride. These implants were injection molded and gamma sterilized in the same way as the above-mentioned poly-L,D-lactide implants containing 50 wt-% calcium nitride.

The mixed and unmixed poly-L,D-lactide implants were installed in the femurs of sheep that were used as test animals. Radiography of the installation area of the implants did not show the implants made of pure poly-L,D-lactide at all. The implants that were mixed with 30 wt-% calcium nitride were weakly visible in the bone tissue. The shape of the implant was not apparent in these radiographs. The implants containing a mixture of 50 wt-% calcium nitride were clearly shown in the radiographs in a way that the base part of the implant as well as also the spiral part were clearly distinguished in the radiographs.

Example 16

Commercial poly-L,D-lactide (manufactured by Boehringer Ingelheim, Germany), silicon carbide (a-SiC:H) and zirconium oxide (ZrO_2, Merck Ltd, Germany) were used to prepare by extrusion (single-screw extruder) a blank with 3 mm thickness, which was cooled down to room temperature on a movable wire. The poly-L,D-lactide was mixed with 10 wt-% silicon carbide and 20 wt-% zirconium oxide in the mass of the poly-L,D-lactide. The blank was cut into rods of 1 m length. The blanks were drawn at 180°C temperature into an oriented blank with a drawdown ratio 7, yielding oriented poly-L,D-lactide blanks of 1.1 mm thickness. The drawn blanks were cut into lengths of 10 mm, which were thermoformed into stud implants as shown in Fig. 6 (diameter 1.1 mm, length 10 mm). The implants were packed in an Aluminium-PET foil pouch and sterilized with gamma radiation.

As comparison materials, implants made purely of poly-L,D-lactide as well as implants made of poly-L,D-lactide mixed with 5wt-% silicon carbide and 10 wt-% zirconium oxide, were used. These implants were extruded, drawn, thermoformed, and gamma sterilized in the same way as the above-mentioned poly-L,D-lactide implants containing 10 wt-% silicon carbide and 20 wt-% zirconium oxide.

The mixed and unmixed implants were used in sheep for testing the fixation of surgically induced rupture of the meniscus. Each implant was tested in two animals. The implants were installed in connection with endoscopy of the meniscus. During the installation, there was direct visual contact with the surgically induced rupture in the meniscus. The implants were triggered with an installation instrument into a preliminary hole made in the tissue of the meniscus. Radiography of the installation area of the implants was performed two days after the installation. The radiography showed clearly the poly-L,D-lactide implants containing 10 wt-% silicon carbide and 20 wt-% zirconium oxide. The implants containing 5wt-% silicon carbide and 10 wt-% zirconium oxide were slightly visible, and the implants made purely of poly-L,D-lactide were not at all shown in the radiographs.

Claims:

1. Surgical implant, device, or part thereof, comprising a mixed combination of at least:

- a bioabsorbable portion of a polymeric material and
- a ceramic particulate portion,

characterized in that the ceramic particulate portion is visible by imaging methods, preferably x-ray positive.

2. Surgical implant, device, or part thereof, as set forth in claim 1, **characterized** in that the x-ray positive ceramic particular portion is mixed into a certain part of the volume of the implant, device, or part thereof.

3. Implant, device, or part thereof, as set forth in claim 1, characterized in that the content of the x-ray positive, ceramic, particulate portion is different in the area of a certain cross-section of the implant, device, or part thereof.

4. Implant, device, or part thereof, as set forth in claim 1, **characterized** in that the x-ray positive particulate portion is selected in a way that it changes, either decelerates or accelerates, the dissolution time of the implant, device, or part thereof, under tissue conditions as compared with the corresponding degradation time of the bioabsorbable implant, device, or part thereof, made of a polymer material.

5. Implant, device, or part thereof, as set forth in claim 1, **characterized** in that the admixture is a ceramic oxide, ceramic sulphate, ceramic phosphate, ceramic nitride or carbide, or a derivative of tri-iodobenzoic acid, or a combination of these.

6. Implant, device, or part thereof, as set forth in claim 1, **characterized**

in that the content of the admixture is 5 to 80 wt-% of the total mass of the implant, advantageously 10 to 60 wt-% and preferably 20 to 50 wt-°4 of the total mass of the implant.

7. Implant, device, or part thereof, as set forth in claim 1, **characterized** in that it is intended for supporting and/or connecting or separating tissues or cut and/or damaged tissues and/or for keeping a tissue cavity open.

8. Implant, device, or part thereof, as set forth in claim 1, **characterized** in that it consists of at least one, at least partly bioabsorbable elongated piece, either a straight piece or a piece twisted at least partly at least once around a center of rotation into a spiral form.

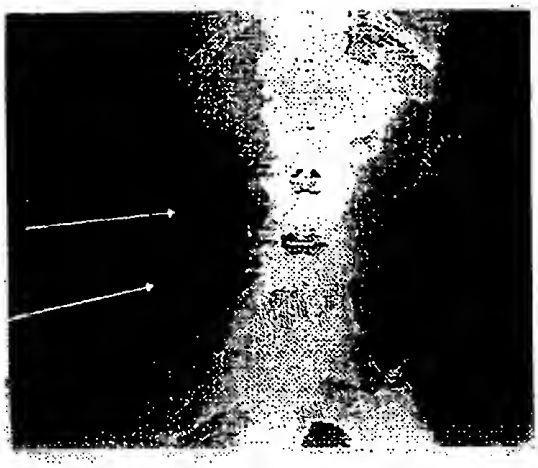

FIG.1

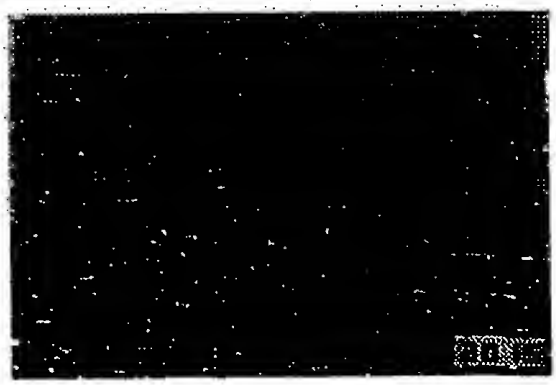

FIG.4

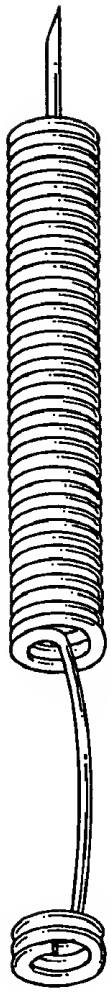

FIG. 2

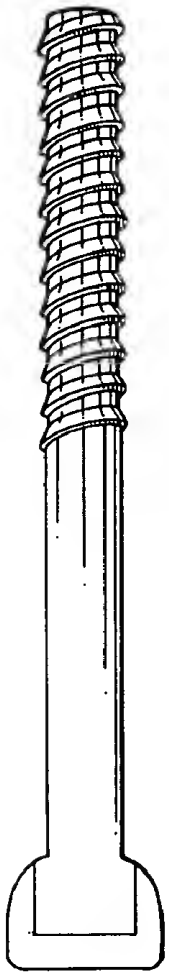

FIG. 3

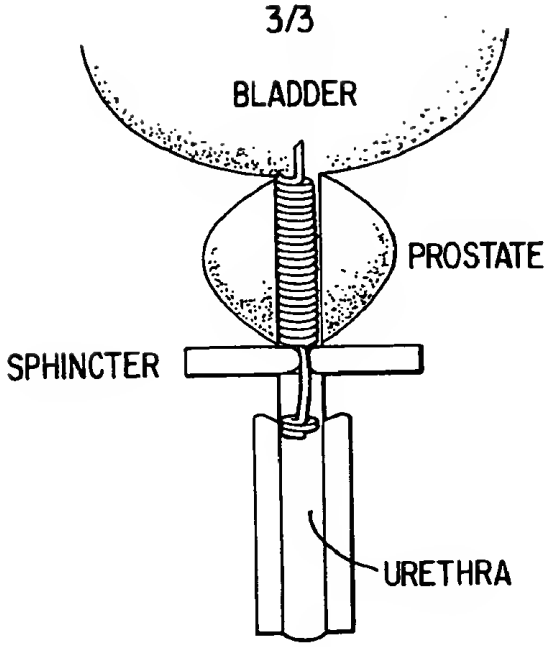

FIG. 5

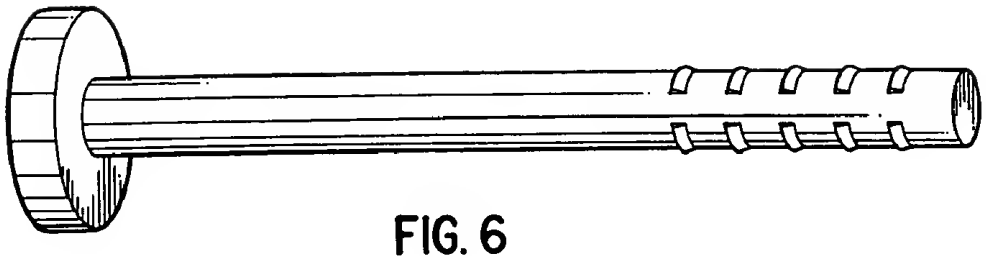

FIG. 6

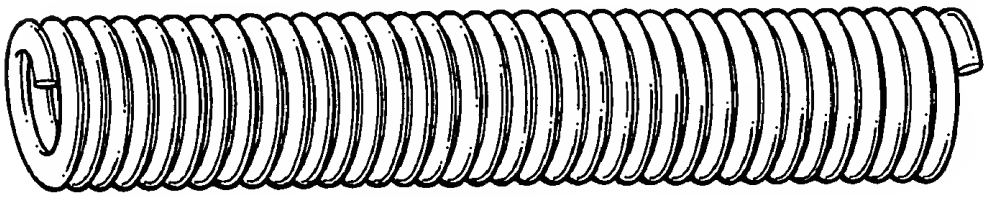

FIG. 7

INTERNATIONAL SEARCH REPORT

Inte. ...nal Application No
PCT/IB 97/01321

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61F2/06 A61L27/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classdication system followed by classification symbols)
IPC 6 A61F A61L A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 34 21 155 A (LEITZ ERNST; KULZER & CO) 12 December 1985 see abstract ---	1,5-8
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☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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1

Date of the actual completion of theinternational search	Date of mailing of the international search report
5 February 1998	16/02/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Hagberg, A

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Inter ...nal Application No
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